ALSDAC MEETING

Thursday, September 13, 2001
Afternoon Session

Opiate Analgesic Use in Pediatric Patients

Pediatric vignettes

EXAMPLE #1:

A pharmaceutical company is developing a novel long-acting sustained release narcotic tablet for the long-term treatment of moderate to severe pain. They are planning two large clinical trials in adults with malignant and non-malignant pain. The sponsor proposes to satisfy the pediatric rule by completing a single multiple dose pharmacokinetic study in children over 7 years of age. Although they will be examining VAS pain scores in these children, efficacy is not a primary endpoint of this study because the sponsor believes that efficacy can be extrapolated from the adult data and that there are not reliable tests of efficacy in children.

In addition, they have asked for a waiver of the pediatric study requirement in children 7 years old and younger for the following reasons:

A. They do not anticipate a "substantial use" of this product in this age group, and they feel that they would not be able to recruit enough patients for such study.
B. They believe that the lowest dose to be marketed would be dangerously high in this age group.
C. They believe that children this age would not reliably be able to take a tablet.

Points to consider:

1. Efficacy endpoints in pediatric age groups
2. Use of long-acting opiates in children
3. Recruitment of pediatric patients for long term analgesic trials
4. Under the terms of the Pediatric Rule, the Agency has the authority to require studies of a new formulation if needed in the pediatric population. The sponsor argues that a formulation appropriate for younger children, such as a syrup, would not retain the sustained-release properties of the investigational drug. Furthermore, as other oral liquid preparations of immediate release opiates are available on the market, an immediate release preparation of their drug would not provide a meaningful therapeutic benefit over existing medications. In addition, they have no plans to market such a formulation.
   --Discuss the value of requiring studies of a pediatric formulation in this setting.
5. Discuss the appropriateness of formulations such as tablets and capsules for children of different age groups. How should issues of size and shape be considered?

EXAMPLE #2:

A pharmaceutical company is developing a new opiate delivery system that gives continuous subcutaneous delivery of a previously approved intermediate-duration opioid with additional patient-activated boluses on demand. Although the drug substance has been approved in other formulations, there is currently no pediatric indication for this drug. The device consists of a reservoir that is adherent to the skin, with a 25G needle that would run from the reservoir into the patient's subcutaneous tissue. The anticipated indication is for moderate to severe pain of at least 24 hours duration. The sponsor plans to conduct two phase III trials in adults for post-operative pain relief and for relief of chronic malignant pain. They have requested a waiver of pediatric studies in children 12 years and under because they believe that this product can not be administered safely in children – i.e. it would get dislodged and the needle would be exposed. Furthermore, they believe that young children would not be able to use the patient-activated demand function appropriately. Finally, the device can only deliver a fixed bolus amount, a dose which would be too large for a small child.

Points to consider:

1. Appropriate pediatric age groups for
   a. Continuous infusion devices
   b. Patient-controlled dosing
   c. Needle delivery devices
   d. Devices applied externally over a period of time
2. Discuss the value of mandating studies of a pediatric-appropriate formulation of this drug (e.g. oral, IV) that would not utilize the subcutaneous injection device

EXAMPLE #3:

A pharmaceutical company is developing a new fixed-dose opioid-acetaminophen combination drug. The drug will be used for acute and chronic treatment of moderate to severe pain. They request a waiver of pediatric studies because they believe that such combination drugs are not appropriate for children, due to the potential for toxicity from large doses of the acetaminophen. In addition, their IRB has expressed concern that analgesic trials in children, particularly placebo-controlled trials, would be unethical.

Points to consider:

1. Appropriateness and dosing considerations for fixed-dose opioid combination drugs in children
2. Ethical concerns surrounding the participation of children in analgesic clinical trials. Do these concerns preclude the participation of children in certain types of analgesic trials (e.g. placebo-controlled)? Do these concerns preclude the participation of certain age groups?

Opioid Formulations Currently Available

	POWDER	INJECTABLE	ORAL										TRANSDERMAL	NASAL	RECTAL
			concentrate	solution	suspension	suspension XR	syrup	elixir	tablet	tablet XR	capsule	capsule XR	lozenge	film XR		suppository
methadone	x	x	x	x			x		x							
meperidine		x					x		x							
meperidine/atropine		x														
codeine combinations				x	x		x		x		x					
morphine		x								x		x				
hydromorphone		x		x					x							
hydrocodone combinations						x	x	x	x		x					
oxycodone combinations				x					x	x	x					
fentanyl		x											x	x		
fentanyl/droperidol		x														
sufentanil		x														
alfentanil		x														
remifentanil		x														
buprenorphine		x													x	
levorphanol		x							x							
butorphanol		x													x	
pentazocine combinations		x							x							
nalbuphine		x														
nalmefene		x														
oxymorphone		x														x
propoxyphene combinations					x				x		x					
tramadol									x							